REMARKS

Claims 74-76 are currently pending in this application. Claim 75 has been amended to address the Examiner's claim objection.

Claim objection

Applicants have amended claim 75 and the specification at page 18 to include SEQ ID NOS for the nucleotide sequences and respectfully request that the objection be withdrawn.

Rejection Under 35 U.S.C. §103

Claim 74 has been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Kauffman *et al.* U.S. Patent No. 5,723,323 (hereinafter "Kauffman") in view of de la Cruz *et al.* (1988), and Shigekawa *et al.* Claim 76 has been rejected under 35 U.S.C. §103 as allegedly being unpatentable over Kauffman in view of de la Cruz *et al.* (1988), Shigekawa *et al.*, and further in view of Donegan *et al.* (1989). The Applicants traverse the rejection and respectfully request reconsideration by the Examiner in light of the following.

In order to establish a *prima facie* case of obviousness, the PTO must satisfy three requirements.

First, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Wilson*, 424 F. 2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970); M.P.E.P. § 2142.

Second, there must be some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); M.P.E.P. § 2142; *Cf. Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 U.S.P.Q.2d 1161 (Fed. Cir. 1999).

Third, the proposed modification of the prior art must have a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q. 1016, 1023 (Fed. Cir. 1991), *cert. denied*, 502 U.S. 856 (1991); *In re Erlich*, 22 U.S.P.Q. 1463, 1466 (Bd. Pat. App. & Int. 1992); *In re Dow Chem.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531.

Applicants are aware of the recent decision *KSR International Co. v. Teleflex Inc.* (U.S.S.C. 2007) which reviewed the law with regard to obviousness. The Court did not reject the use of "teaching, suggestion or motivation" as a factor in the obviousness analysis. Rather the Court recognized that a showing of "teaching suggestion or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight.

Here, the references when combined fail to teach or suggest all of the claim elements. Furthermore, even if the combination of the references did teach or suggest all of the claim elements, there is not a reasonable expectation of success.

A. Claim 74

Claim 74 requires the amino-terminal display of the random peptides of the library. The claim includes the limitation

> wherein each of said different vectors comprises a polynucleotide sequence that encodes a fusion protein comprising a peptide fused to a coat protein of a filamentous bacteriophage so that the N-terminal amino acid of said fusion protein is the N-terminal amino acid of said peptide [Emphasis added]

The combined references cited by the Examiner do not teach or suggest this limitation. Claim 74 is directed to methods of screening fusion phage libraries in which the epitopic peptide is fused directly to the N-terminal amino acid of the phage coat protein. By contrast, de la Cruz *et al.* discloses a method of epitope expression in which repeats of the circumsporozoite protein were introduced into bacteriophage DNA as follows

> [e]pitope expression is accomplished by cloning into the unique *BamH1* restriction enzyme site of a minor coat protein (pIII) gene of the filamentous bacteriophage, f1 (5). The cloning site is located between two functional domains of the protein. The N-terminal portion of pIII binds to the *E. coli* F pilus during infection, while the C-terminal portion is buried in the virion and functions in morphogenesis. [Emphasis added] [page 4320, right column under the Discussion section]

The fusion proteins contemplated by de la Cruz *et al.* have a circumsporozoite peptide inserted between the N- and C- terminal pIII domains. As the N-terminal amino acid of the de la Cruz *et al.* fusion protein is not the N-terminal amino acid of the inserted circumsporozoite peptide, it

does not teach all the limitations of claim 74. In addition, the reference does not suggest this limitation either because it does not refer to any other system for producing fusion proteins.

As acknowledged by the Examiner, Kauffman does not disclose the fusion of random peptides with coat proteins in filamentous bacteriophage expression vectors and Shigekawa concerns electroporation. Therefore, the combined references do not teach or suggest the amino-terminal display limitation of claim 74.

In addition, because the combined references do not teach or suggest the amino-terminal display limitation, there cannot be a reasonable expectation of success in identifying a polynucleotide sequence encoding a peptide which binds to a preselected receptor molecule, because Applicants have shown that the amino-terminal display is part of a successful method. As such, a prima facie case of obviousness has not been established and Applicants respectfully request the withdrawal of this rejection.

B. Claim 76

Claim 76 recites a method of identifying a polynucleotide sequence encoding a peptide which binds to a preselected receptor molecule that includes the step of selecting bacteriophage particles displaying a peptide by

> selecting bacteriophage particles displaying the peptide by combining said particles with the preselected receptor molecule and separating particles bound to immobilized preselected receptor molecule from unbound particles;
>
> repeating the selection step at least once, wherein the selected bacteriophage particles are propagated between said selection steps and wherein said receptor is immobilized at reduced densities in subsequent repetitions of the selecting step; and [Emphasis added]

The combined references cited by the Examiner do not teach or suggest these limitations. Claim 76 is directed to methods of screening fusion phage libraries in which (i) preselected receptor is immobilized to facilitate binding of random peptides having affinity to the receptor, and (ii) in subsequent selecting steps the density of immobilized receptor is reduced.

As acknowledged by the Examiner, none of Kauffman, de la Cruz *et al.*, or Shigekawa *et*

al. disclose receptor immobilization. The Examiner relies on Donegan *et al.* to support the rejection of claim 76. However, Applicants respectfully submit that Donegan *et al.* fails to cure the defects of the other references because it too fails to teach or suggest all the limitations of claim 76.

(1) Claim 76 requires reduced densities of immobilized receptor.

Reducing the density of immobilized receptor in subsequent screening steps is advantageous because it allows for the enrichment of phage that display peptides with high affinity for the immobilized preselected receptor. The enrichment occurs because while higher densities promote multivalent interactions, reduced densities favor a monovalent interaction between a high affinity peptide and the immobilized receptor. A multivalent interaction is one in which a phage bearing peptide binds to more than one receptor binding site resulting in the high peptide avidity and tenacious adherence of the phage during washing. While it may be appropriate to promote multivalent interactions in the initial screening rounds to reduce the background of non-specifically bound phage, subsequent screening rounds under conditions favoring monovalent interactions allows for the identification of the highest affinity peptides. Claim 76 requires immobilized receptors at reduced densities in subsequent selection rounds, which in turn allows the identification of peptides having high affinity for the receptor.

(2) Donegan et al. does not disclose all the limitations of claim 76.

By contrast, Donegan *et al.* does not teach or suggest a reduction in the density of immobilized material in subsequent rounds of selection. The reference only discloses the preparation of nitrocellulose filters by applying 1-2 μg of chromosomal DNA and subsequent hybridization screening with recombinant phage stock (see page 17 and 18). In addition, the reference does not suggest the reduced density limitation either because it discloses no other amounts of chromosomal DNA. The filters were prepared using the same 1-2 μg of chromosomal DNA in the primary, secondary, tertiary, and final screening rounds (see page 18-20). As such, Donegan *et al.* does not teach or suggest a reduction in the density of immobilized material, *i.e.*, genomic DNA from *N. gonorrhoeae* or *N. meningitidis*.

Therefore, the combined references do not teach or suggest the reduced density of immobilized receptor limitation. In addition, because none of the references teach the reduced density limitation, there cannot be a reasonable expectation of success in identifying a polynucleotide sequence encoding a peptide which binds to a preselected receptor molecule, because Applicants have shown that the reduced density of immobilized receptor is part of a successful method. As such, a prima facie case of obviousness has not been established and Applicants respectfully request the withdrawal of this rejection.

Nonstatutory obvious-type double patenting rejection

Claims 74-76 stand rejected under the judicially created doctrine of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1, 39, and 40 of Kauffman *et al.* U.S. Patent No. 5,723,323. The Examiner argues that claims 1, 39 and 40 of Kauffman differ from pending claims 74-76 in that they do not recite the last step of polynucleotide sequencing. Applicants respectfully traverse this rejection and submit that the pending claims are patentably distinct over the claims of Kauffman because the Examiner has not taken into account all the limitations of the pending claims.

Claim 74

As explained in response to the 103 rejection above, the method recited in claim 74 recites a method of screening fusion phage libraries in which the epitopic peptide is fused directly to the N-terminal amino acid of the phage coat protein. None of the Kauffman claims cited by the Examiner include this limitation. As such, claim 74 is patentably distinct over Kauffman.

Claim 75

Claim 75 recites a method of screening fusion phage libraries in which a single-stranded oligonucleotide capable of efficient ligation into a double-stranded filamentous phage vector. The central component of the oligonucleotide encodes a variant peptide, while the flanking components specify nucleotides used to reconstruct suitable restrictions endonuclease sites in the cloning vector. Figure 1 illustrates the procedure for inserting such a single-stranded nucleotide

into a double-stranded vector. Briefly, the oligonucleotide recited in claim 75 is annealed with two "half-site" oligonucleotides to form BstXI cohesive ends. The resulting partially-single stranded molecule is then ligated into a BstXI-digested vector. This method is advantageous because it provides for efficient ligation of a single-stranded oligonucleotide into a double-stranded vector, and it avoids the need to digest oligonucleotides encoding random peptides to achieve cohesive ends. None of the Kauffman claims cited by the Examiner include this limitation. As such, claim 75 is patentably distinct over Kauffman.

Claim 76

As explained in response to the 103 rejection above, the method recited in claim 76 recites a method of screening fusion phage libraries in which the density of immobilized receptor is reduced in subsequent screening steps. None of the Kauffman claims cited by the Examiner include this limitation. As such, claim 76 is patentably distinct over Kauffman.

Since the invention claimed in the instant case is patentably distinct over claims 1, 39, and 40 of Kauffman et al., the Examiner is respectfully requested to reconsider and withdraw the present rejection.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **44368-0001**).

Respectfully submitted,

Date: July 12, 2007

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